divided into 4 subgroups (Table). Conclusion: Measuring the combination of TnT and BNP after optimized treatment may be valuable for risk assessment of cardiac mortality and morbidity in CHF pts.

Risk stratification using discharge values of TnT and BNP

Subgroup	I (T-/B-) n=37	II (T-/B+) n=20	III (T+/B-) n=9	IV (T+/B+) n=27
Cardiac death	0 (0%)	0 (0%)	2 (22%)	7 (26%)
Cardiac event	5 (14%)	6 (30%)	4 (44%)	21 (78%)

POSTER SESSION

1015 Cardiomyopathy Models and Hypertrophic Cardiomyopathy

Sunday, March 17, 2002, 9:00 a.m.-11:00 a.m.
Georgia World Congress Center, Hall G
Presentation Hour: 9:00 a.m.-10:00 a.m.

1015-137 Compensated Cardiac Hypertrophy in Endothelial Nitric Oxide Synthase Knockout Mice

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Background: It is well documented that endothelial nitric oxide synthase (eNOS) homozygous knockout mice ($eNOS^{-/-}$) develop sustained arterial hypertension. Because of controversy over the development of cardiac pathophysiology in these mice, we undertook to investigate the cardiac functional and biochemical effects of chronic eNOS ablation.
Methods: We examined steady state levels of molecular markers of cardiac hypertrophy and heart failure in male $eNOS^{-/-}$ and control mice at 18-20, 27-30, 40 and 52 weeks of age. Histological examination at 40 weeks of age and cardiac functional analysis using the isolated work performing heart preparation were performed at 52 weeks of age.
Results: Hearts from $eNOS^{-/-}$ mice exhibited concentric left ventricular hypertrophy, multifocal replacement fibrosis and evidence of myocyte degeneration/death. As mice aged, re-induction of atrial natriuretic factor (ANF) and α-skeletal-actin mRNA correlated positively with the degree of cardiac hypertrophy. Significant increases in cardiac expression of tumor necrosis factor-α (TNF-α) mRNA and protein were detected at 27-30 weeks. Sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) transcript levels were markedly decreased at 27-40 weeks, whereas hearts of $eNOS^{-/-}$ mice 52 weeks of age demonstrated normalized SERCA2a and slightly decreased phospholamban protein levels. Although hearts of $eNOS^{-/-}$ mice at 52 weeks of age demonstrated no deficit of baseline function, there was a blunted response to β-adrenergic stimulation indicative of reduced contractile reserve.
Conclusions: Although $eNOS^{-/-}$ mice exhibit myocardial remodeling, including re-induction of cardiac fetal genes and dysregulation of TNF-α and SERCA2a, there is no progression to failure before 52 weeks of age and in fact these hearts are hypercontractile. An increased ratio of SERCA2a protein to phospholamban protein at this timepoint suggests a mechanism for the long-term physiological compensation that occurs in $eNOS^{-/-}$ hearts.

1015-138 New Mutation in Lamin A/C Gene Associated With Severe Dilated Cardiomyopathy

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Background: Idiopathic Dilated Cardiomyopathy (DCM) is familial in about 30% of the cases. Lamin A/C mutations have been identified for causing familial DCM, frecuently associated with conduction system disease. We report here a novel lamin A/C mutation with features of severe dilated cardiomyopathy.
Methods: After informed consent, we studied the lamin A/C gene in 17 patients of 14 different families with familial DCM. DNA was isolated from frozen blood samples and coding regions of lamin A/C were PCR amplified, studied by SSCP and cycle sequenced.
Results:Three members of one of the families (mother and her two female identical twins) developed severe DCM and required cardiac transplantation at 36, 18, and 20 years old respectively. The father of the index case had died suddenly at 52 years old. At diagnosis, the mother was on atrial fibrillation with slow ventricular response. No conduction disturbance was present in the twins.
A new mutation (Arg349Leu) was identified in exon 6 in the three patients. This mutation was not present in 22 unaffected relatives and in more than 100 healthy controls. This mutation affects a highly conserved region identical in Xenopus laevis, Gallus gallus, Rattus norvegicus and humans.
Conclusions: The Arg349Leu mutation in LMNA A/C gene is associated with a severe form of DCM.

1015-139 Cyclosporine A Treatment Decreases Left Ventricular Mass in Mice Expressing a FHC-Linked Troponin T (I79N) Mutation

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Cyclosporine A (CyA) prevents cardiac hypertrophy in several animal models, and has been proposed as treatment for Familial Hypertrophic Cardiomyopathy (FHC). But with the recent report that CyA administration increased cardiac hypertrophy and mortality in a mouse model of FHC (αMHC+/403), proposed clinical studies with CyA were abandoned. Because the CyA effect could be specific to this particular mouse model, we examined the effect of CyA in a different murine FHC model expressing a troponin T (I79N) mutation. **Methods**: Mice expressing human wild-type (Tg-WT), mutant (Tg-I79N) Troponin T and non-transgenic littermates (Non-Tg) were treated with CyA (18mg/kg/day) or vehicle for 4 weeks. LV dimensions, mass and function were measured with serial echocardiography in blinded fashion. **Results:** All mice tolerated CyA treatment. LV wall thickness and mass significantly **decreased** in CyA-treated Tg-I79N mice compared to all other groups (table). Systolic function was unchanged. On sacrifice, heart to body weight ratio was significantly decreased in CyA-treated compared to vehicle-treated Tg-I79N mice, (3.3±.1mg/g vs. 3.6±0.1mg/g, p<.05). No significant differences in tissue histology were found. Blood CyA levels were 453±124 ng/ml. **Conclusion:** Unlike in mice expressing a α-myosin heavy chain FHC mutation, CyA treatment **reduced** LV mass in mice expressing a FHC-linked Troponin T mutation. Thus, any effect of CyA treatment should not be generalized across different FHC-linked mutation or models.

Effect of CyA treatment on LV-mass (means±se)

Genotype	n	Treatment	Baseline (mg)	4 weeks (mg)
Tg-I79N	7	CyA	84±3	72±4**
Tg-I79N	7	Vehicle	85±6	118±4
Tg-WT	6	CyA	100±3	112±5
Non-Tg	6	CyA	87±3	111±8

1015-140 Effect of Estrogen on Angiotensin Receptors, Matrix Metalloproteinases, and Left Ventricular Mass in a Transgenic Mouse Model of Human Hypertrophic Cardiomyopathy

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Background: Mutations in α-tropomyosin (Asp175Asn) can cause familial hypertrophic cardiomyopathy (FHCM). Estrogen has been shown to be cardioprotective in several diseases. This study was designed to determine whether estrogen in physiological doses can modify left ventricular (LV) function and hypertrophy by attenuating release of matrix metalloproteinases (MMPs) and by regulating angiotensin receptors (AT_1) in a transgenic mouse model (TGM) expressing Asp175Asn.
Methods: TGM and nontransgenic cohorts (NTGM) (20 each) were ovariectomized (ov). Slow-release (90 days) estrogen pellets were implanted in 10 mice of each group; the other 10 received placebo. Echocardiograms were performed in awake mice at 2 weeks after ov (baseline) and after 3 months of daily treadmill exercise. LV mass was assessed from M-mode tracings. Mice were then euthanized and some hearts were perfusion-fixed and embedded in paraffin, for sectioning; others were processed for frozen sections and tissue extracts. Immunohistochemical staining and immunoblotting were performed.
Results: Intact TGM and NTGM had LV masses of 77 and 49 mg, and placebo-treated and estrogen-treated ov TGM had LV masses of 79 and 60 mg, respectively ($p<0.05$, for both comparisons). AT-1 receptors, MMP-3 and MMP-13 were increased in untreated ov TGM compared to estrogen-treated ov TGM.
Conclusions: Estrogen replacement significantly reduced LV mass, AT-1 receptors and MMP-3 and MMP-13 in a model of FHCM. These findings suggest that estrogen can regulate expression of genes involved in matrix metabolism and cardiac fibrosis, which are of clinical importance in human patients with FHCM.

1015-159 Determinants of Exercise Capacity in Hypertrophic Cardiomyopathy: The Role of Left Ventricular Outflow Tract Obstruction

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Background: The influence of left ventricular outflow tract obstruction (LVOTO) on exercise capacity in patients (pts) with Hypertrophic Cardiomyopathy (HCM) is poorly understood.
Methods: 86 pts with HCM (43 ±14yrs, 73% symptomatic) underwent upright bicycle ergometry with expiratory gas analysis and echocardiography. Oxygen consumption at peak exercise (pkVO2), anaerobic threshold (atVO2); O2 pulse at peak exercise (pkO2 pulse), anaerobic threshold (atO2 pulse); and peak workload are expressed as percentage of predicted values.
Results: 37 pts with resting LVOTO >=30mmHg (58 ±20mmHg, group A), had a lower pkVO2 than those without resting LVOTO, 65 ±19 vs 74 ±19%, p=0.03. In pts without resting LVOTO, pkVO2 correlated with peak exercise LVOTO (r=0.43, p=0.003) and change in LVOTO during exercise (r=0.44, p=0.002). Of 49 pts without resting LVOTO, 16 developed LVOTO >30mmHg during exercise (group Bi), 33 did not (group Bn). Peak exercise LVOTO was lower in group Bi than group A (48 ±21 vs 81 ±27mmHg, p<0.001). Table 1.
There was no difference between the 3 groups for peak heart rate and respiratory quo-